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Effects of bicarbonate- and lactate-buffered replacement fluids on cardiovascular outcome in CVVH patients

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Effects of bicarbonate- and lactate-buffered replacement fluids on cardiovascular outcome in CVVH patients.

Background. Bicarbonate-buffered replacement fluid (RF-bic) in continuous venovenous hemofiltration (CVVH) may be superior to lactate-buffered replacement fluid (RF-lac) in acute renal failure. In an open, randomized, multicenter study, we investigated the effects of RF-bic and RF-lac on cardiovascular outcome in patients requiring CVVH following acute renal failure.

Methods. One hundred seventeen patients between the age of 18 and 80 years were randomized to CVVH either with RF-bic ($N = 61$) or RF-lac ($N = 56$). Patients were treated with CVVH for five days or until either renal function was restored or the patient was removed from the study. Data were analyzed on day 5 or according to the "last observation carried forward" (LOCF) option. Adverse events were classified according to the WHO-Adverse Reaction Terminology system.

Results. Blood lactate levels were significantly lower and blood bicarbonate levels were significantly higher in patients treated with RF-bic than in those treated with RF-lac (lactate, 17.4 ± 8.5 vs. 28.7 ± 10.4 mg/dL, $P < 0.05$; bicarbonate, 23.7 ± 0.4 vs. 21.8 ± 0.5 mmol/L, $P < 0.01$). The number of hypotensive crises was lower in RF-bic–treated patients than in RF-lac–treated patients (RF-bic 14 out of 61 patients, RF-lac in 29 out of 56 patients; 0.26 ± 0.09 vs. 0.60 ± 0.31 episodes per 24 h, $P < 0.05$). Nine out of 61 patients (15%) treated with RF-bic and 21 out of 56 patients (38%) treated with RF-lac developed cardiovascular events during CVVH therapy ($P < 0.01$). A multiple regression analysis showed that the occurrence of cardiovascular events was dependent on replacement fluid and previous cardiovascular disease and not on age or blood pressure. Patients with cardiac failure died less frequently in the group treated with RF-bic (7 out of 24, 29%) than in the group treated with RF-lac (12 out of 21, 57%, $P = 0.058$). In patients with septic shock, lethality was comparable in both groups (RF-bic, 10 out of 27, 37%; RF-lac, 7 out of 20, 35%, P = NS).

Conclusions. The results show that the administration of RF-bic solution was superior in normalizing acidosis of patients without the risk of alkalosis. The data also suggest that the use of RF-bic during CVVH reduces cardiovascular events in critically ill patients with acute renal failure, particularly those with previous cardiovascular disease or heart failure.

Key words: acute renal failure, dialysate, renal replacement fluid, hemofiltration, blood lactate, glucose, heart failure, cardiovascular disease.

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Despite extensive clinical experience with dialysis in acute renal failure and many technical advances in the delivery of extracorporeal care over the past decades, the mortality rate of critically ill patients with acute renal failure requiring dialysis therapy remains high [1–3]. The persistent high mortality has been attributed to a reduction of cases with uncomplicated isolated acute renal failure and an increase of patients with multiple organ dysfunction syndrome, including acute renal failure [4]. One goal of continuous renal replacement therapy is to maintain normal or near normal acid-base balance in patients with acute renal failure, thereby preventing detrimental effects of acidemia on cardiovascular performance, hepatic metabolism, and hormonal response [5]. In conventional hemofiltration solutions, lactate, which is converted to bicarbonate on an equimolar basis under physiological conditions, is used as the buffer to correct acidosis [5]. However, there are several studies suggesting that lactate can exert negative effects on metabolic and on hemodynamic parameters [5–7]. In critically ill patients with multiple organ dysfunction, conversion of lactate to bicarbonate is often diminished, and lactatemia caused by lactate infusion may have negative effects. The possibility of bicarbonate-buffered replacement fluids (RF-bics) has been pointed out as an alternative that may improve the prognosis of critically ill patients with acute renal failure [8–10]. However, to date there are no randomized studies comparing the effects of RF-bics and lactate-buffered replacement fluids (RF-lacs) on prognosis. The objective of the present study was to test the hypothesis of whether the use of RF-bic in continuous venovenous hemofiltration (CVVH) is superior in preventing cardiovascular complications to RF-lac. In an open, multicenter, randomized study, we investigated the

Table 1. Composition of the replacement fluids

	RF-bic		RF-lac	
	Free of K^+	With K^+	Free of K^+	With K^+
Na^+	140	140	135	135
K^+	0	2	0	2
Ca^{2+}	1.5	1.5	1.88	1.875
Mg^{2+}	0.5	0.5	0.75	0.75
Cl^-	109	111	106.5	108.5
HCO_3^-	35	35	—	—
Lactate	—	—	33.75	33.75
Glucose	5.6	5.6	7.5	8.3

Values are mmol/L.

effects of RF-bic and RF-lac on cardiovascular outcome in patients requiring CVVH following acute renal failure.

METHODS

We conducted an open, randomized, multicenter study. The investigation was approved by the ethics committee of the University of Muenster. The patients or the patients' next of kin gave written informed consent to participate in this trial. Patients who developed acute renal failure and who were treated at an medical intensive care unit were considered for enrollment into the study. During a screening period, which took place within 24 hours prior to the start of continuous hemofiltration, patients were to be evaluated for eligibility. During this period, the inclusion and exclusion criteria, medical history, complete medical examination, and laboratory parameters were evaluated. The clinical status was assessed by the APACHE II classification system. To be eligible for participating in the study, male or female patients had to be between 18 and 80 years of age. Inclusion criteria were the development of acute oliguric or anuric renal failure, acute azotemia, or acute deterioration of renal function associated with volume overload refractory to diuretic therapy. Patients who met the following criteria were excluded from study participation: chronic renal failure (serum creatinine level >3 mg), serum lactate levels >45 mg/dL (>5 mmol/L), blood pH <7.30, malignant disease, pregnancy, or lactation. One hundred seventeen patients were included into the study. The randomization lists were generated by the computer program RANCODE version 3.1 (Gauting, Munich, Germany). Sixty-one patients were randomized to CVVH using a RF-bic, 56 patients to CVVH using RF-lac. Since the RF-bic had to be prepared by mixing a base solution (4000 mL) and an electrolyte solution (500 mL) immediately before administration, a blinding procedure was technically not possible. The replacement fluids were manufactured by Fresenius Medical Care (Bad Homburg, Germany). The final composition of the replacement fluids is shown in Table 1.

Continuous venovenous hemofiltration was performed after the patient had been carefully examined. Vascular access was obtained by femoral or jugular vein catheterization. Patients received machine hemofiltration using commercially available hollow-fiber hemofilters with a blood flow rate limited to a maximum of 200 mL/min. Anticoagulation was achieved with heparin, given in doses to maintain an activated partial thromboplastin time between 100 and 150 seconds. The replacement fluids containing 2 mmol/L K^+ or potassium-free solutions were chosen by the attending physicians on the basis of the patient's serum potassium values. Temperature of the replacement fluids was adjusted at 36.5°C. Rates of ultrafiltration and fluid replacement were approximately 1000 mL/hour. Arterial blood pressure was monitored throughout treatment using a radial or femoral arterial catheter. Vasopressor therapy was chosen by the attending physicians in order to treat heart failure and to elevate the blood pressure in hypotensive states. Patients were treated with continuous hemofiltration for five days or until either renal function was restored or the patient was withdrawn from the study because of adverse events or medical judgment of the investigators. In either of these cases, a final assessment of the patient's status was performed before the patient was removed from the study. Data were analyzed on day 5 or according to the "last observation carried forward" (LOCF) option. Adverse events were classified according to the WHO-ART system [11].

Clinical data and laboratory parameters were evaluated according to the study protocol. The fluid volume status was assessed by the attending physician based on clinical examination, x-ray of the chest and hemodynamic parameters determined by central venous pressure, and, in some patients, right heart catheterization. The following data were documented once daily at 6 p.m.: clinical status, clinical complications, diuresis per 24 hours, frequency of hypotensive episodes (defined as systolic blood pressure drop below 70 mm Hg), daily fluid balance, infusion site, and anticoagulation. Blood count, serum creatinine, serum urea, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (γ-GT), total protein, and fibrinogen levels were also determined once daily. Respiratory rate, central venous pressure, electrolytes, glucose, lactate, and activated clotting time (ACT) were evaluated twice daily, at 6 p.m. and at 6 a.m. Blood flow, ultrafiltration, substitution volume, body temperature, heart rate, systolic and diastolic blood pressure, and blood gas analysis were documented four times daily (6 p.m., 12 p.m., 6 a.m., and 12 a.m.). The study was regularly controlled by monitors. The monitor checked the data entered in the clinical report forms in order to verify adherence to the study protocol. Data obtained in the study were entered into a computer database (Access 2.0).

Table 2. Baseline clinical characteristics

Variable	RF-bic	RF-lac	*P*
N	61	56	
Age *years*	59 ± 15	64 ± 10	NS
Weight *kg*	79 ± 14	80 ± 15	NS
Height *cm*	172 ± 9	71 ± 8	NS
Gender *female/male*	15/46	16/40	NS
APACHE II score	26 ± 1.0	27 ± 0.9	NS
Blood pressure *mm Hg*	117 ± 3/59 ± 2	114 ± 4/58 ± 2	NS
Heart rate/*min*	106 ± 3	107 ± 3	NS
Temperature *°C*	37.7 ± 0.18	38.0 ± 0.16	NS
Central venous pressure *cm H_2O*	13 ± 1	11 ± 1	NS
Number of patients on pressure support	56 (92%)	48 (87%)	NS
Number of patients on ventilator support	55 (90%)	49 (89%)	NS
Number of patients with multiorgan failure	6 (10%)	4 (7%)	NS
Number of patients with relevant previous disease			
Respiratory tract	25 (41%)	21 (38%)	NS
Cardiovascular system	41 (67%)	43 (77%)	NS
Coronary artery disease	26 (43%)	24 (43%)	NS
Other cardiac disease	8 (13%)	10 (18%)	NS
Previous operation	47 (77%)	43 (77%)	NS
Medication previous to acute renal failure	50 (82%)	46 (82%)	NS
Causes of acute renal failure			
Cardiovascular disease	26 (43%)	27 (48%)	NS
Thereof acute heart failure	24 (39%)	21 (38%)	NS
Sepsis	30 (49%)	23 (41%)	NS
Metabolic	5 (8%)	6 (11%)	NS

Data are mean ± SEM. Abbreviations are: RF-bic, bicarbonate-buffered replacement fluid; RF-lac, lactate-buffered replacement fluid; NS, not significant.

Statistics

Statistical analysis was performed by a statistical institute (Harrison Clinical Research, Munich, Germany). Data were expressed as mean ± SEM. Statistical comparisons between the groups were carried out using the *t*-test for continuous variables and the chi-square test for qualitative variables. A multiple logistic regression analysis was used to assess the independent relationship between treatment and cardiovascular outcome. Values of $P < 0.05$ were considered to be statistically significant.

RESULTS

Baseline characteristics of the groups treated with RF-bic and with RF-lac in venovenous hemofiltration therapy are shown in Table 2. Age tended to be higher in the group treated with RF-lac than in the group treated with RF-bic, but the difference was not statistically significant. There were no differences in gender, weight, height, and APACHE II score at baseline. Blood pressure, heart rate, temperature, and central venous pressure were also similar in both groups at baseline. The proportion of patients with ventilator or pressure support and multiorgan failure was not different between both study groups. Relevant previous diseases and medications given prior to the onset of acute renal failure were comparable in both groups (Table 2). Acute renal failure was due to cardiovascular disease and sepsis in most patients. There were no significant differences in the causes of acute renal failure between the study groups (Table 2). Laboratory parameters at baseline are shown in Table 3. There were no significant differences of laboratory values at baseline between the group treated with RF-bic and RF-lac (Table 2).

Table 3. Baseline laboratory parameters

Variable	RF-bic	RF-lac	*P*
N	61	56	
Blood pH	7.37 ± 0.01	7.39 ± 0.01	NS
Blood bicarbonate *mmol/L*	23 ± 0.8	23 ± 0.8	NS
Blood base excess (BE)	−0.98 ± 0.71	−1.03 ± 0.91	NS
pCO_2 *mm Hg*	42 ± 2	39 ± 2	NS
pO_2 *mm Hg*	106 ± 8	93 ± 4	NS
Blood lactate *mg/dL*	24.5 ± 2.9	26.4 ± 2.5	NS
Hemoglobin *g/dL*	10.8 ± 0.3	10.9 ± 0.3	NS
Serum creatinine *mg/dL*	3.3 ± 0.2	3.8 ± 0.3	NS
Serum urea-N *mg/dL*	132 ± 12	146 ± 14	NS
ALT *U/L*	213 ± 91	142 ± 62	NS
AST *U/L*	255 ± 148	169 ± 66	NS
γ-GT *U/L*	75 ± 15	58 ± 8	NS
Total protein *g/L*	51.7 ± 1.3	51.4 ± 1.1	NS
Fibrinogen *mg/dL*	495 ± 24	561 ± 27	NS
Glucose *mg/dL*	187 ± 10	186 ± 11	NS

Data are mean ± SEM.

The hemofiltration regimen was comparable between both study groups. Hemofiltration was applied for 3.64 ± 0.2 days in RF-bic–treated patients versus 3.40 ± 0.2 days in RF-lac–treated patients (P = NS). Mean blood flow was 137 ± 7 mL/min in RF-bic–treated and 132 ± 7 mL in RF-lac–treated patients (P = NS). The mean 24-hour ultrafiltration rate was 28794 ± 2193 mL in RF-bic–treated and 31472 ± 2100 mL in RF-lac–treated

Table 4. Clinical and biochemical parameters at end of the study

Variable	RF-bic	RF-lac	*P*
N	61	56	
APACHE II score	26 ± 1.0	27 ± 0.9	NS
Blood pressure *mm Hg*	124 ± 3/62 ± 2	129 ± 4/60 ± 2	NS
Heart rate min^{-1}	102 ± 2	99 ± 3	NS
Temperature *°C*	37.3 ± 0.12	37.2 ± 0.10	NS
CVP *cm* H_2O	9.8 ± 0.7	10.5 ± 0.7	NS
Mean respiratory rate min^{-1}	20.5 ± 2.0	23.4 ± 2.1	NS
Mean PEEP *cm* H_2O	6.3 ± 0.39	5.9 ± 0.40	NS
Blood bicarbonate *mmol/L*	23.7 ± 0.4	21.8 ± 0.5	< 0.01
Blood lactate *mg/dL*	17.4 ± 8.5	28.7 ± 10.4	< 0.05
Intravenous bicarbonate (1 mmol/mL, mL/24 h)	13 ± 7	68 ± 39	< 0.01
Mean pH	7.37 ± 0.01	7.39 ± 0.01	NS
pCO_2 *mm Hg*	38.3 ± 0.8	37.4 ± 1.1	NS
pO_2 *mm Hg*	96 ± 3	102 ± 4	NS
Mean blood base excess (BE)	−0.6 ± 0.4	−2.2 ± 0.5	< 0.01
Hemoglobin *g/dL*	10.7 ± 0.3	10.4 ± 0.3	NS
Serum creatinine *mg/dL*	2.6 ± 0.3	2.3 ± 0.2	NS
Serum urea-N *mg/dL*	109 ± 9	107 ± 11	NS
ALT *U/L*	88 ± 28	56 ± 16	NS
AST *U/L*	70 ± 18	40 ± 16	NS
γ-GT *U/L*	112 ± 18	89 ± 14	NS
Total protein *g/L*	56.7 ± 1.8	55.9 ± 1.6	NS
Fibrinogen *mg/dL*	509 ± 31	490 ± 38	NS
Glucose *mg/dL*	162 ± 9	182 ± 10	NS

Data are mean ± SEM. Abbreviations are: CVP, central vein pressure; PEEP, positive endexpiratory pressure; i.v., intravenously; BE, base excess.

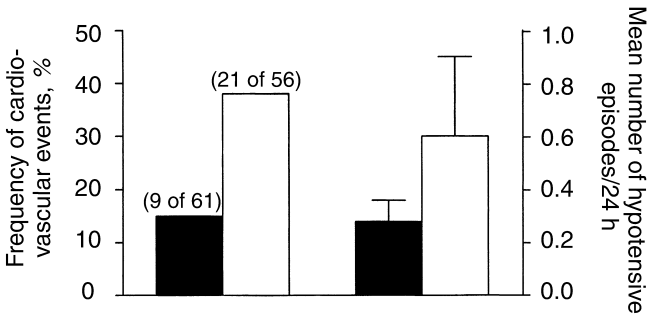

Fig. 1. Frequency of cardiovascular events and mean number of hypotensive episodes per 24 hours before the end of the study in patients with acute renal failure treated with bicarbonate-buffered (■; RF-bic; *N* = 61) and lactate-buffered (□; RF-lac; *N* = 56) replacement fluids during continuous venovenous hemofiltration (CVVH).

patients (*P* = NS). The mean 24-hour substitution volume was 26476 ± 2044 mL in RF-bic–treated and 28985 ± 2727 mL in RF-lac–treated patients (*P* = NS). Net ultrafiltration and ultrafiltration/kg body weight was 2325 ± 191 mL and 29 ± 3 mL/kg in RF-bic–treated patients versus 2490 ± 218 mL and 31 ± 3 mL/kg in RF-lac–treated patients (*P* = NS). The mean diuresis did not differ between both groups. Diuresis was 1254 ± 257 mL/24 hour in the RF-bic–treated and 1587 ± 403 mL/24 hour in the RF-lac–treated group (*P* = NS).

Clinical parameters and laboratory data on day 5 or according to the LOCF option are shown in Table 4. Blood pressure levels and heart rate were not significantly different between both study groups. Serum bicarbonate levels were significantly lower in the patients treated with RF-lac than in those treated with RF-bic ($P < 0.01$). This held true despite the fact that patients treated with RF-lac received significantly more intravenous bicarbonate than patients treated with RF-bic replacement fluid (Table 4). Blood lactate levels were significantly lower in RF-bic–treated than in the RF-lac–treated patients ($P < 0.05$).

Cardiovascular complications during hemofiltration therapy were observed less frequently in the group treated with RF-bic as compared with the group treated with RF-lac. Nine out of 61 (15%) RF-bic–treated patients and 21 out of 56 (38%) RF-lac–treated patients developed cardiovascular complications during hemofiltration ($P < 0.01$; Fig. 1). The number of hypotensive episodes was lower in the group treated with RF-bic than in the group treated with RF-lac. Fourteen hypotensive events were observed in the RF-bic–treated group, and 29 hypotensive episodes were observed in the RF-lac–treated group during the last 24 hours before the end of the study. On average, the mean number of hypotensive episodes was significantly lower in RF-bic–treated as compared with RF-lac–treated patients ($P < 0.05$; Fig. 1). The incidence of hypotension was 0.26 ± 0.09 episodes/24 hours in RF-bic–treated patients and 0.60 ± 0.31 episodes/24 hours in RF-lac–treated patients.

Forty-four (38%) patients died during the study period. In the group treated with RF-bic, 20 of 61 (33%) patients died during hemofiltration therapy, and in the group treated with RF-lac, 24 of 56 (43%) patients died (*P* = NS). The mortality rate just failed to be significantly different between both study groups in patients with cardiac failure. Seven of 24 (29%) patients with cardiac failure died in the group treated with RF-bic, while 12 of 21 (57%) patients with cardiac failure died in the group treated with RF-lac ($P = 0.058$). In patients with sepsis, mortality was comparable in both groups. Ten of 27 (37%) septic patients died in the group treated with RF-bic, and 7 of 20 (35%) septic patients died in the group treated with RF-lac (*P* = NS).

The logistic regression analysis showed that the occurrence of cardiovascular events during hemofiltration therapy was dependent on the administered replacement fluid and previous cardiovascular disease, and not on age or blood pressure (Table 5). There was a significant relationship between the development of cardiovascular events and the type of replacement fluid used during hemofiltration ($P < 0.01$). The effects of the replacement fluid on cardiovascular complications were independent of previous cardiovascular disease and age. The relation-

Table 5. Logistic regression analysis for the occurrence of cardiovascular events (dependent variable)

Independent variable	Correlation coefficient	*t*-value	*p*-value
Replacement fluid (RF-bic/RF-lac)	0.217	8.259	0.0041
Cardiovascular disease prior to enrollment	0.209	7.840	0.0051
Age *years*	0.106	3.397	0.065
Body mass index kg/m^2	−0.346	2.158	0.141
APACHE II score	0.033	0.050	0.147
Hemoglobin level at baseline *g/L*	0.000	0.213	0.821
Temperature at baseline *°C*	0.000	0.146	0.702
Systolic blood pressure at baseline *mm Hg*	0.000	0.491	0.483
Diastolic blood pressure at baseline *mm Hg*	0.000	0.087	0.767
Heart rate/ *min*	0.000	0.020	0.882
Blood bicarbonate at baseline *mmol/L*	−0.059	1.099	0.294
Blood lactate level at baseline *mg/dL*	0.000	0.102	0.749
Serum creatinine level at baseline *mg/dL*	−0.059	2.473	0.111
Serum urea at baseline *mg/dL*	0.081	2.870	0.092

ship between cardiovascular complications and replacement fluid was also independent of the APACHE II score at baseline, temperature, blood pressure, heart rate, hemoglobin, blood bicarbonate, blood lactate, serum creatinine, and serum urea-N concentrations at baseline. The presence of previous cardiovascular disease was a significant independent predictor for the development of cardiovascular events ($P < 0.01$; Table 5). There was also a relationship between the development of cardiovascular complications during hemofiltration therapy and age, but the relationship just failed to reach statistical significance ($P = 0.065$). The cardiovascular event rate was not related to baseline APACHE II score, blood pressure, heart rate, temperature, blood bicarbonate, blood lactate, hemoglobin, serum creatinine, and serum urea-N concentrations (Table 5).

DISCUSSION

The objective of the present randomized study was to investigate whether the use of RF-bic in CVVH would improve cardiovascular outcome in critically ill patients with acute renal failure when compared with RF-lac. The results presented here clearly demonstrate that cardiovascular events during CVVH occurred less frequently in patients treated with RF-bics as compared with patients treated with RF-lacs. The number of hypotensive episodes was also lower in patients treated with RF-bics than with RF-lacs. The beneficial effect of RF-bic on the development of cardiovascular events was independent of age and previous cardiovascular disease in the logistic regression analysis. Moreover, our data also suggest that RF-bic during hemofiltration may decrease mortality in patients with cardiac failure, whereas the death rate was comparable between bicarbonate- and lactate-treated septic patients. The data of the present study confirm previous studies showing that the administration of RF-bics during hemofiltration is superior in normalizing acidosis when compared with RF-lacs [9, 10].

Lactate is used in commercially available replacement fluids employed for continuous hemofiltration therapy as the buffer to correct acidosis. Under physiological conditions, the resulting exogenous lactate load of 40 to 45 mmol/L during continuous hemofiltration can be converted to bicarbonate on an equimolar basis by the liver [12]. However, in conditions in which lactate overproduction occurs or the conversion pathways are impaired, such as in hypoxic states or circulatory failure, in preexisting lactic acidemia or in patients with liver failure, complications may arise from the use of lactate-based replacement fluids [13, 14]. The use of RF-bic during CVVH has therefore been recommended in patients with lactic acidemia and severe liver failure [5, 6]. However, in the present study, patients with lactic acidemia were not enrolled, and most patients had normal liver function at entry into study. Thus, the data of the present trial suggest that the use of RF-bics should also be recommended in critically ill patients with normal blood lactate levels or liver function.

The exogenous lactate load during continuous hemofiltration should be taken in the context of the hypermetabolic, hypodynamic, or hyperdynamic cardiovascular and systemic inflammatory state of critically ill patients. This syndrome of critically ill patients is characterized by excess production of lactate even in the absence of lactatemia, increased oxygen consumption, and elevated protein catabolism with increased urea nitrogen production [15–17]. There is some evidence that the administration of large amounts of lactate can also result in an increased protein catabolic rate [18]. The adverse effects of RF-lac on protein catabolism can be attributed to an increased lactate:pyruvate ratio [18]. It has been shown that excessively elevated lactate:pyruvate ratios can promote liver glucose production at the expense of amino acids in isolated hepatocytes, thus increasing protein catabolism [19]. Since protein catabolic rates are already excessively increased in critically ill patients with acute renal failure, this abnormality may be exacerbated by the administration of large lactate loads. The increase in the intracellular lactate:pyruvate ratio was also been associated with a rise in adenosine diphosphate (ADP) levels and depletion of cellular energy stores, which can impair oxygen delivery and left ventricular function [7, 20].

It has been shown that high amounts of administered lactate result in an increase in intracellular lactate con-

centrations, which is associated with a reduction in myocardial performance [21]. Nimmo, Grant, and Mackenzie demonstrated that the increase in blood lactate levels during hemofiltration with RF-lacs was associated with a concomitant decline of cardiac index [22]. It has therefore been suggested that the possible hemodynamic disadvantages of lactate buffering may be avoided by the use of bicarbonate-buffered solutions [1, 5, 6]. The negative effects of RF-lacs on cardiac performance are consistent with the findings of our study showing that the use of RF-bics was associated with a lower rate of cardiovascular events, which could be mainly attributed to low cardiac performance. Moreover, mortality rate tended to be lower in bicarbonate-treated patients with cardiac failure as compared with lactate-treated patients with cardiac failure, whereas mortality was similar in both groups of septic patients. This observation indicates that RF-bics may be particularly superior to RF-lacs in patients with a reduced cardiac performance. However, it was beyond the scope of the present study to elucidate possible mechanisms responsible for a lower cardiovascular event rate in the group treated with RF-bic. Up to now, there are only a few studies that have compared the effect of different buffers used in replacement fluids on hemodynamics. Thomas et al investigated the influence of a lactate- and bicarbonate-buffered solution on hemodynamic parameters by right catheter measurements in 41 patients with acute renal failure before and 24 hours after hemofiltration [23]. They observed no differences of cardiac index, left ventricular stroke work index, and oxygen consumption for RF-lacs and RF-bics. In that study, acute renal insufficiency caused by acute heart failure occurred in only 2 out of 40 patients as compared with 45 of 117 patients in our study. In a cross over design, Kierdorf et al investigated the effect of lactate- and bicarbonate-buffered solutions on arterial blood pressure and the need of positive inotropic substances in 20 patients with acute renal failure [24]. There was no difference in mean arterial blood pressure or in the need of positive inotropic substances. In this study, the number of patients with heart failure was also considerably smaller than in our study.

In conclusion, the results of the present study confirm that the administration of RF-bics during hemofiltration is superior in normalizing acidosis when compared with lactate-buffered solutions. The results also show that CVVH with RF-bics can reduce cardiovascular events in critically ill patients with acute renal failure. Our data suggest that the use of RF-bics during CVVH in acute renal failure is preferable to RF-lacs in critically ill patients with acute renal failure, particularly those with previous cardiovascular disease or heart failure.

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REFERENCES

1. Himmelfarb J: Dialytic therapy in acute renal failure: No reason for nihilism. *Semin Dial* 9:230–234, 1996
2. Kierdorf HP, Sieberth HG: Continuous renal replacement therapies versus intermittent hemodialysis in acute renal failure: What do we know? *Am J Kidney Dis* 28(Suppl 3):S90–S96, 1996
3. Chew SL, Lins RL, Daelemans R, DeBroe ME: Outcome of acute renal failure. *Nephrol Dial Transplant* 8:101–107, 1993
4. Cameron JS: Acute renal failure thirty years on. *Q J Med* 74:1–2, 1990
5. Macias WL: Choice of replacement fluid/dialysate anion in continuous renal replacement therapy. *Am J Kidney Dis* 28(Suppl):S15–S20, 1996
6. Davenport A, Will E, Davison AM: The effect of lactate-buffered solutions on the acid-base status of patients with renal failure. *Nephrol Dial Transplant* 4:800–804, 1989
7. Veech L: The untoward effects of the anions of dialysis fluid. *Kidney Int* 34:587–597, 1988
8. Reynolds HN, Belzberg H, Connelly J: Hyperlactemia in patients undergoing continuous arteriovenous hemofiltration with dialysis. *Crit Care Med* 18:582–587, 1990
9. Gudis SM, Mangi S, Feinroth M, Rubin JE, Friedman EA, Berlyne GM: Rapid correction of severe lactic acidosis with massive isotonic bicarbonate infusion and simultaneous ultrafiltration. *Nephron* 33:65–66, 1983
10. Vaziri ND, Ness R, Weilikson L, Barton C, Greep N: Bicarbonate-buffered peritoneal dialysis: An effective adjunct in the treatment of lactic acidosis. *Am J Med* 67:392–396, 1979
11. Edwards R, Danan G, Biriell C, Benichou C: Proposed improvement to the WHO Adverse Reaction Terminology (WHO-ART). *Pharmacoepidemiol Drug Safety* 2:177–184, 1993
12. Connor H, Wood HF, Murray JG, Ledingham JG: Utilisation of L(+) lactate in patients with liver disease. *Ann Nutr Metab* 26: 308–314, 1982
13. Woll PF, Record CO: Lactate elimination in man: Effects of lactate concentration and hepatic dysfunction. *Eur J Clin Invest* 9:397–404, 1979
14. Kruse JA, Zaidi SAJ, Carlson RW: Significance of blood lactate levels in critically ill patients with liver disease. *Am J Med* 83:77–82, 1987
15. Cerra FB: Metabolic manifestations of multiple systems organ failure. *Crit Care Clin* 5:119–131, 1989
16. Kruse JA, Carlson RW: Lactate metabolism. *Crit Care Clin* 3: 742–747, 1987
17. Mizock BA: Alterations in carbohydrate metabolism during stress: A review of the literature. *Am J Med* 98:75–84, 1995
18. Veech RL: The toxic impact of parenteral solutions on the metabolism of cells: A hypothesis for physiological parenteral therapy. *Am J Clin Nutr* 44:519–551, 1986
19. Sistare FD, Haynes RC: Acute stimulation by glucocorticoids of gluconeogenesis from lactate/pyruvate in isolated hepatocytes

from normal and adrenalectomized rats. *J Biol Chem* 23:12754–12760, 1985

20. Panichi V, Parrini M, Bianchi AM, Andreini B, Cirami C, Finato V, Palla R: Mechanism of acid-base homeostasis in acetate and bicarbonate dialysis, lactate hemofiltration and hemodiafiltration. *Int J Artif Organs* 17:315–321, 1994
21. Saman S, Opie LH: Mechanism of reduction of action potential duration of ventricular myocardium by exogenous lactate. *J Mol Cell Cardiol* 10:659–662, 1984
22. Nimmo GR, Grant IS, Mackenzie SJ: Lactate and acid base changes in the critically ill. *Postgrad Med J* 67(Suppl I):S56–S61, 1991
23. Thomas AN, Guy JM, Kishen R, Geraghty IF, Bowles BJM, Vadgamna P: Comparison of lactate and bicarbonate buffered haemofiltration fluids: Use in critically ill patients. *Nephrol Dial Transplant* 12:1212–1217, 1997
24. Kierdorf HP, Leue C, Heintz B, Riehl J, Melzer H, Sieberth HG: Continuous venovenous hemofiltration in acute renal failure: Is a bicarbonate- or lactate-buffered substitution better? *Contrib Nephrol* 116:38–47, 1995